REMARKS

Claims 42, 43, and 45 stand currently amended and claims 42, 43, 45, 46, and 47 are now pending. The amendments are fully supported by the claims as filed and no new matter is believed to have been added.

Claims 42-43 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

Claims 42-43 also stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement for allegedly including new matter.

Claim 45 stands rejected under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 45-51 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ball et al. (WO 95/34578) in view of Vrtala et al. (1996. J. Allergy Clin. Immun., Vol. 97(3): 781 - 787).

Claims 42 - 43 and 45 also stand rejected under 35 U.S.C. § 1112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The above amendments and the following remarks have addressed all the grounds for rejection and/or objection or have otherwise rendered them moot. Applicants respectfully request the Examiner reconsider all outstanding rejections, and that they be withdrawn.

Rejection under 35 U.S.C. § 112, First Paragraph

Claims 42-43 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

The Examiner asserts that the claims recite "a" polynucleotide as part of the invention and that the specification does not teach a single nucleotide having the ability to encode the fusion polypeptide consisting of timothy grass pollen allergens.

Applicants respectfully differ with the Examiner's hypertechnical reading of the claims as written. Applicants are at a loss as to how "a polynucleotide" can be read to mean "a single nucleotide" in the Examiner's construction. Using the article "a" does not in anyway negate the fact that Applicants are referring to a set or sequence of nucleotides, much as one can speak in terms of "a class", "a group", "a set" and be generally understood to be referring to a plurality of elements having at least one common characteristics. Nevertheless, Applicants have amended the claims to refer to "a polynucleotide sequence" to erase any ambiguity that the Applicants are referring to a plurality of nucleotides encoding the polypeptide of interest.

The claims as written are specifically directed to a method of preparing fusion polypeptides consisting of timothy grass pollen allergens using a polynucleotide sequence encoding the same. The specification is replete with teachings of how to accomplish the claimed methodology exemplified by the pollen allergens rPhl p 1, rPhl p 2, rPhl p 5, rPhl p 6 etc. Applicants respectfully ask the Examiner to treat claims 42 and 43 as method claims which they are, and not product claims, and to erase from her consideration set, the requirement that Applicants must disclose the primary structure of every single polynucleotide amenable to the claimed methodology. Since the Examiner's basis for rejection and her entire argument is based on the Applicants recitation of " "a" polynucleotide", it is believed that the basis for the rejection have now been completely obviated by the amendment of the claims in question to recite "a polynucleotide

sequence" commensurate with the teachings of the specification. Applicants respectfully request that this ground for rejection be withdrawn.

Claim 42 also stands rejected as failing to meet the written description requirement because it recites that the "immunotherapeutic agents induce stronger immune responses compared with the individual components or mixtures thereof." The Examiner asserts that there is insufficient teaching on how to obtain such a mixture. Referring to page 3 of the specification for support, Applicants have amended the claim to refer to "fragments thereof" in the sense that the hybrid allergen can be a hybrid of the naturally occurring allergens or a hybrid of fragments of the naturally occurring allergens, said fragments obtainable by means already known in the art such as by restriction and ligation of the coding nucleotide sequence. Again, with the understanding that claim 42 is a method claim and not a product claim, it is respectfully asserted that the said amendment has obviated this ground for rejection and it should therefore be withdrawn.

The Examiner further asserts that the Applicants did not disclose a preparation method but rather "disclosed the entire sequences but have failed to disclose a method for preparing a hybrid polypeptide as recited." Applicants do not understand whether "as recited" refers to the Examiner's hypertechnical construction of "a polynucleotide" as referring to "a single nucleotide" encoding a hybrid polypeptide. Applicants do not believe that it is scientifically possible for "a single nucleotide" to encode a polypeptide.

Other than that, Applicants believe that the specification adequately describes a method of preparing a hybrid polypeptide using hybrid polynucleotide sequences encoding said hybrid polypeptide. The Examiner is referred to Figure 2 wherein the method of producing a hybrid polynucleotide of Phl p 5 and Phl p 1 is reduced to drawing. On page 11, Example 2, Applicants describe in detail how to construct

recombinant hybrid allergens. On page 13, Example 3, Applicants describe how to obtain a recombinant hybrid polypeptide using the recombinant hybrid polynucleotide sequences of Example 2.

In view of the foregoing, it is respectfully asserted that claim 42 as amended is adequately described and enabled by the instant specification; there being no further basis for maintaining this ground for rejection, it should therefore be withdrawn.

Claims 42-43 also stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement for allegedly including new matter. The Examiner asserts that neither the specification nor the originally presented claims provide support for a method of preparing fusion polypeptides consisting of timothy grass pollen allergens for use as immunotherapeutic agents comprising an (sic) provision step; an introduction step; a culturing step; a recover (sic) step; and testing the fusion polypeptide as candidate immunotherapeutic agents by administering said polypeptide to a test animal and selecting as immunotherapeutic agents those fusion polypeptides that induce IgE-blocking antibodies and induce stronger immune responses compared with the individual components or mixtures thereof.

A copy of the instant specification is provided herewith for the Examiner's convenience. Support in the specification for the basic steps of claim 42 is enumerated as follows:

(a) providing a polynucleotide sequence encoding the fusion polypeptide: See Figure 2. See also Example 2, page 11, paragraphs.
(b) introducing said polynucleotide sequence into a host cell: See Example 3, Page 13 using E. coli as a host cell.
(c) culturing the host cell obtained in b) under conditions such that the fusion polypeptide is expressed: See Example 3, page 13, paragraph 3.

(d) recovering the expressed fusion polypeptide from the cultured host cell: See Example 3, page 13, paragraph 4.

(e) testing the fusion polypeptide as candidate immunotherapeutic agents by administering said polypeptide to a test animal and selecting as immunotherapeutic agents those fusion polypeptides that induce IgE-blocking antibodies and induce stronger immune responses compared with the individual components or ~~mixtures~~ fragments thereof: See Example 5, page 15.

See also Example 6, page 16.

In view of the foregoing, Applicants believe that there is no basis for maintaining this ground for rejection and respectfully request that it be withdrawn.

Rejections 35 U.S.C. § 112, second paragraph

Claim 45 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner asserts that there is insufficient antecedent basis for "the respective wild-type allergens" in the claims.

Applicants have amended the claims in some cases to obviate the use of that term and in other cases to try to impact more clarity to the claims. It should be pointed out that the failure to provide explicit antecedent basis for terms does not always render a claim indefinite. If the scope of a claim would be reasonably ascertainable by those skilled in the art, then the claim is not indefinite. MPEP 2173.05(e).

The phrase, "wild-type" is understood in the art to refer to the "outside the laboratory" hence wild-type, as in naturally occurring as opposed to genetically engineered variants of a given protein. The offending phrase, "wild-type" has been deleted and it is respectfully asked that this ground for rejection should be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

Claims 45-47 (claims 48 – 51, having been previously canceled) stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ball et al. (WO 95/34578) in view of Vrtala et al. (1996. J. Allergy Clin. Immun., Vol. 97(3): 781 - 787). According to the Examiner, Ball et al. teach that the major grass pollen Phl p1 can be part of a hybrid or fusion polypeptide but does not specifically recite using another plant allergenic protein within the hybrid polypeptide. To cure the deficiency in Ball, the Examiner asserts that Vrtala et al., teach that DNA coding for three major timothy grass pollen allergens representing group I (Phl p1), group II (Phl p2) and group V(Phl p5) was known. Therefore, concludes the Examiner, "it would have been prima facie obvious at the time of applicants' invention to modify the plant polypeptide as taught by Ball et al., to include a different plant allergen as taught by Vrtala et al., to create a hybrid plant fusion allergen wherein said allergen is a fusion protein of two or more timothy grass pollen allergens." Applicants respectfully disagree and traverse as follows.

The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that the combination should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art. Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure. In re Dow Chemical Co., 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir, 1988). In determining whether such a suggestion can fairly be gleaned from the prior art, the full field of the invention must be considered for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention. As a matter of law, therefore, the mere fact that the prior art could be so modified would not make the modification obvious unless the prior art suggested the desirability of the modification. In re Laskowski, 871 F.2d 115, 10 USPQ2d 1397 (Fed. Cir. 1989).

The Ball et al. reference is equivalent to U.S. Patent No. 6,008,340. Applicants refer the Examiner to the following excerpt which captures the entire teaching of Ball et al. with respect to fusion proteins of Phl p1 epitopes and expressible polypeptides.

> A fourth aspect of the invention is a recombinant or synthetic protein or polypeptide displaying the antigenicity of a Phl p I epitope, in particular comprising as an essential part a Phl p I epitope of at least one of the sequences set out in SEQ ID NOS: 5, 7 and 9-28. The protein or polypeptides may be fused to an additional polypeptide, such as beta galactosidase, GST or lambda cII protein or **any other polypeptide that can be expressed as a fusion protein** in prokaryotic or eukaryotic cells. U.S. 6,008,340 Col. 2, ln 64 -67; Col. 3, ln 1-6.

Per the above excerpt, Ball et al. teach the expression of Phl p1 epitopes fused with expressible proteins in order to amplify the expression of the Phl p1 epitope and to aid in downstream isolation, purification and homogenization of the expressed protein.

The Examiner's assertion that Ball et al. already teach the need to have a hybrid or fusion polypeptide is not a proper Section 103(a) motivation for the instant invention.

There is no suggestion, teaching, motivation, express or implied in the Ball et al. disclosure that the fusion protein of Phl p1 epitopes and **expressible proteins** can be used for therapeutic purposes. Ball et al. taught the fusion of Phl p1 and expressible proteins for the purposes of enhancing the expression and isolation of Phl p1. If anything, the administration of Ball's fusion protein comprising **Phl p1 and expressible proteins** will cause severe anaphylactic reaction in recipients. In fact, Ball et al. teach away from administering any other allergen other than well defined epitopes of Phl p1 (as opposed to crude allergen extract) and in no way suggested using a fusion protein of hybrid allergens as therapeutic agents. Applicants are at a great loss as to where the Examiner cites for her motivation

For that matter, the hybrid fusion allergens of the present invention may be fused with expressible proteins in order to amplify the expression of the hybrid fusion allergens and facilitate the isolation, purification and homogenization of those allergens. That technology of amplifying expression of desirable proteins by fusing them with expressible proteins is old and well known. The Examiner is referred to the following teaching from the Ball et al. patent.

> The Phl p I epitope encoded by clone 98 was expressed as a beta - galactosidase fusion protein in liquid culture (**Huynh et al., 1985**) and was affinity purified using an anti-beta-galactosidase affinity column. (Promega, Maddison, USA) as described (Vrtala et al., 1993a). U.S. 6,008,340 Col. 5, ln 59 -65.

The Huynh et al., (1985) reference at least stands for the teaching that the fusion of proteins with expressible proteins is not new and Ball et al. taught no more than the fusion of Phl p1 epitopes with expressible proteins merely to amplify the expression of, and to aid in isolation of proteins of therapeutic interest. .

Prior to the current invention, no one has taught nor suggested that the fusion of hybrid allergens can produce immunotherapeutic agents more desirable than the respective component allergens. That such is the case was indeed a surprise to the inventors who are leading researchers in this area. The Rule 132 declaration submitted prior affirmed the inventor's surprise that fusion proteins of naturally occurring allergens can be used as immunotherapeutic agents and exhibit increased immunogenicity. That surprising discovery at least negates the finding of obviousness on the basis of the Ball et al. and Vrtala et al. combination.

On the basis of the foregoing, Applicants respectfully assert that the above combination is improper and that this ground for rejection should be withdrawn.

New Ground for Rejection: 35 U.S.C. § 112, second paragraph

Claims 42 - 43 and 45 also stand rejected under 35 U.S.C. § 1112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 42, the Examiner asserts that there is no antecedent basis for "the individual components or mixtures thereof" Applicant's respectfully disagree. A fusion polypeptide is **inherently** a fusion of individual components or fragments thereof. The inherency doctrine obviates this ground for rejection. Applicants welcome the Examiner's suggestion by way of Examiner's amendment to what at this point is the Applicants' best effort to clearly and distinctly claim that which they have invented.

Regarding claim 45, the Examiner asserts that it is unclear how a wild-type allergen which naturally has one allergen can comprise a fusion of allergens. Again, the fusion allergen of the present invention comprises **(or is comprised of)** wild-type allergen and wild-type allergens comprise the fusion allergen of the present invention. Applicants have no appreciation for the Examiner's difficulty with the fact that a composition (so to say) is comprised of components and components comprise a composition. Again, Applicants welcome the Examiner's suggestion by way of Examiner's amendment to what at this point is the Applicants' best effort to clearly and distinctly claim that which they have invented.

CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office action and, as such, the present application is in condition for allowance. Applicants wish to expedite the prosecution process and if the Examiner believes, for any reason that personal

communication will help expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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